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Speculations on the Viral Etiology of Acquired Immune Deficiency Syndrome and Kaposi's Sarcoma

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The acquired immune deficiency syndrome (AIDS) appeared in the United States in late 1978 and has spread at an epidemic rate through the four major coastal cities of this country. The disease appears to show the same epidemiologic distribution as hepatitis B virus infection, and for this reason, most investigators feel that this new disease is caused by a blood-borne sexually transmitted virus.

A number of viral agents have been suggested as the cause of AIDS, but to date, no virus has been consistently isolated. The most likely candidate is a retrovirus that has recently been introduced into the human population and has found its way into two extremely high-risk groups, namely, promiscuous male homosexuals and intravenous drug abusers.

The relationship between Kaposi's sarcoma and cytomegalovirus is still unclear, but evidence is mounting that cytomegalovirus may be the agent that initiates this multifocal malignancy. Multiple factors must be involved in this process. It is known that some immunosuppressed individuals develop Kaposi's sarcoma, which completely resolves when the immunosuppression is reversed; however, in individuals with classical Kaposi's sarcoma, the profound degree of helper T-cell depression that characterizes the acquired immune deficiency syndrome is not seen.

WHERE DID THE AIDS EPIDEMIC COME FROM?

In 1872, the Hungarian dermatologist Moritz (Kohn) Kaposi described multiple idiopathic hemorrhagic sarcoma [1], a rare multifocal sarcoma that generally begins as small violaceous papules and nodules on the lower extremities of elderly men. These lesions enlarge and coalesce to form plaques, nodules, and tumors, which untreated can reach giant configurations. The tumors are generally red or purple in hue in light-skinned individuals and purple to brownish in dark-skinned individuals. As the lesions become older, they darken in color, progressing from red to dark purple to brown. Lesions may be 10 cm or larger and may number from one to hundreds in a single patient. The lesions generally begin on the lower extremities, but they can also been seen on the upper extremities, and scattered lesions can occur on the trunk, head, neck, and genitalia. Nodules and tumors may cluster along veins, especially on the lower extremities. Early lesions are not palpable, but as the lesions age, they become rubbery and compressible. Generally, lesions are asymptomatic, but patients can experience burning, itching, or pain. Edema of the lower legs is common and is generally of the persistent or brawny type rather than pitting in nature. The edema may be so severe as to restrict walking. Lesions will occasionally outgrow their blood supply and show central infarction and regression.

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Abbreviations:
AIDS: acquired immune deficiency syndrome
CMV: cytomegalovirus
EBV: Epstein-Barr virus
HTLV: human T-cell leukemia virus

Internal organs can be involved. The most common lesions are in the mouth and gastrointestinal tract. Lesions have been described on the tonsils and in the lungs, adrenal glands, spleen, liver, kidney, pericardium, and bone. Occasionally, the disease will be exclusively visceral without cutaneous lesions. Death generally occurs from generalized disease with cachexia, hemorrhage, or impairment of vital organ function by tumor proliferation [2–5].

The disease did not receive widespread attention until the 1960s, when it was recognized that large numbers of cases of Kaposi's sarcoma occur in equatorial Africa. This area is primarily composed of open bush country and rolling hills. The altitude is between 1200 and 1500 m. The region includes Uganda, Kenya, Tanzania, and Zaire. Kaposi's sarcoma in this area is strikingly frequent, comprising between 3% and 10% of all malignant tumors as compared with only 0.02% of malignancies reported in the United States. The African cases were extensively studied by Templeton and Huh [6]. In addition to the classical nodular presentation, three additional clinical presentations were recognized—an exophytic or florid form, an infiltrative form, and a lymphadenopathic form. The nodular type was the most common and may coexist with other aggressive forms of Kaposi's sarcoma. The nodular type is generally indolent and shows a variable response to chemotherapy. Spontaneous remissions were seen. The exophytic or florid variety was usually rapid growing; ulceration, secondary infection, and hemorrhage were common. These tumors may extend deep into the dermis and involve underlying muscle or bone. Generally, the exophytic or florid form responds dramatically to chemotherapy. The infiltrative type usually occurs on an extremity and shows deep invasive penetration of tumor into muscle and bone. These lesions are generally of long duration and respond poorly to chemotherapy. The lymphadenopathic type occurs most commonly in children and is often rapidly progressive. This form, of course, is easily confused with a lymphoma. Because of the rapid growth of these lesions, the prognosis was generally poor until aggressive chemotherapy was introduced. Recent reports have indicted a favorable response to chemotherapy with some long-term survivors [7].

The histologic pattern of each of these types of Kaposi's sarcoma is useful in predicting the natural history of the disease and the patient's response to therapy [8]. As seen in Table I, the nodular and lymphadenopathic forms of Kaposi's sarcoma show a histologic picture composed of both spindle cells and numerous vascular slits. The infiltrative form shows a monocellular histologic pattern composed predominantly of spindle cells and frequent plasma cells. The exophytic or florid type shows both mixed cells and monocellular patterns with occasional anaplastic presentation.

In the 1970s it was also realized that Kaposi's sarcoma was seen as an opportunistic malignancy in individuals who were iatrogenicly immunosuppressed [9,10]. Two reports were presented as confirmation that the immunosuppression was pivotal to the appearance of the disease—one a case of temporal arteritis and the other a case of asthma—both were treated with prednisone and Kaposi's sarcoma developed after the patient was immunosuppressed [11]. In both instances, the corticosteroids were discontinued and the Kaposi's sarcoma totally regressed as the patient's immune system recovered.

TABLE I. *Correlation between gross and microscopic tumor morphology in 37 Ugandan patients*

Tumor type	Histologic pattern		
	Mixed cell	Monocellular	Anaplastic
Nodular	9	1	0
Florid	6	7	3
Infiltrative	1	4	0
Lymphadenopathic	6	0	0

Source: From Taylor et al [8].

TABLE II. *Acquired immune deficiency syndrome (AIDS): Weekly surveillance report of U.S. cases reported to CDC (November 15, 1983)*

Primary disease[a]	Cases	Percent of total	Deaths	Percent dead
KS without PCP	722	26.2	151	20.9
PCP without KS	1407	51.1	644	45.8
Both KS and PCP	193	7.0	113	58.6
OI without KS or PCP	431	15.7	218	50.6
Total	2753	100.0	1126	40.9

[a] KS = Kaposi's sarcoma, PCP = *Pneumocystis carinii* pneumonia, OI = other opportunistic infections.

Source: From AIDS Activity Center for Infectious Diseases [13].

TABLE III. *Distribution of Kaposi's sarcoma and Pneumocystis carinii pneumonia by risk group*

	No. of cases	No. of Kaposi's sarcoma cases (%)	No. of *Pneumocystis* pneumonia cases (%)
Homosexuals	727	342 (47%)	385 (53%)
IV Drug Users	155	6 (4%)	149 (96%)
Haitians	50	2 (4%)	48 (96%)
Hemophiliacs	7	0 —	7 (100%)
Unknown	61	16 (26%)	45 (74%)
	1000		

Source: From H Jaffe, personal communication.

In the summer of 1981, the Centers for Disease Control reported cases of Kaposi's sarcoma from New York and a variety of opportunistic infections from southern California [12]. Both these highly unusual outbreaks were combined as a single report because they shared the epidemiologic features occurring in young homosexual men who had been sexually promiscuous. Thus we were first notified of the appearance of what has come to be called the acquired immune deficiency syndrome (AIDS).

In retrospect, it would appear that there were two or three cases in 1978, 7 or 8 cases in 1979, and then an exponential rise in the number of cases since that time. Currently, there is a doubling of cases every 6 months. By November of 1983, over 2753 cases had been reported in the United States.

Table II shows that half the cases have presented with *Pneumocystis carinii* pneumonia without Kaposi's sarcoma, and only 25% of the cases have presented with Kaposi's sarcoma without *Pneumocystis* pneumonia. What Table II does not show is the striking difference in presentation of disease between the two high-risk groups. Male homosexuals present with *Pneumocystis* pneumonia 53% of the time and Kaposi's sarcoma 47% of the time (Table III). IV drug users have *Pneumocystis* pneumonia 96% of the time and Kaposi's sarcoma only 4% of the time.

Table IV indicates an overall mortality rate of 40%. Unfortunately, this figure is artifically low because of the rapid appearance of new cases. The overall mortality rate of *Pneumocystis carinii* pneumonia approaches 100% by 18 months after the initial diagnosis. The prognosis for patients presenting with Kaposi's sarcoma is somewhat better, with a 20 to 30% survival rate at 2 years.

Table IV shows that half the cases occur in men in the 30–40 age group, with a peak age at about 36. This is intriguing when we recall that the peak age for other sexually transmitted diseases, such as syphilis, gonorrhea, and hepatitis B, is in the midtwenties, a full decade earlier. Does this suggest that some disease such as hepatitis B acquired in the third decade of life predisposes to this new disease in the fourth decade? Could there be other factors introduced in the third decade of life, such as exposure to semen, drugs, or allogenic T-lymphocytes, or the loss of some natural resistance, such as interferon, which predisposes the homosexual patient to the AIDS agent in the next decade of life?

Table V shows the racial/ethnic distribution of American cases. The percentage of blacks suffering from AIDS is higher than the percentage of black people in this country. It is not clear whether this increase is due to a genetic susceptibility of blacks to Kaposi's sarcoma, as suggested by the endemic focus of the disease in equatorial Africa, or because of the high incidence of AIDS among intravenous drug abusers, many of whom are black. San Francisco has the second highest incidence of AIDS in the United States because of its large homosexual population. Twenty-five percent of the population of San Francisco is Asian, and yet we know of only one Asian case occurring in our area. Clearly, epidemiologic studies of Asians is urgently needed to tell us if the Asian homosexual male engages in the same sexual practices and has the same rate of promiscuity as his Caucasian counterpart or if Asians are in some way genetically protected from this new disease.

Table VI shows that most of the cases have been homosexual males and intravenous drug abusers. These percentages have remained constant since the beginning of the epidemic in 1980, indicating that the disease is not spreading to other segments

TABLE IV. *Acquired immune deficiency syndrome (AIDS): Weekly surveillance report of U.S. cases reported to CDC (November 15, 1983)*

Age	Cases	Percent of total
Under 20	13	0.5
20–29	610	22.1
30–39	1280	46.5
40–49	595	21.6
Over 49	247	9.0
Unknown	8	0.3
Total	2753	100.0

Source: From AIDS Activity Center for Infectious Diseases [13].

TABLE V. *Acquired immune deficiency syndrome (AIDS): Weekly surveillance report of U.S. cases reported to CDC (November 15, 1983)*

Race/ethnicity	Cases	Percent of total
White, not Hispanic	1588	57.7
Black, not Hispanic	713	25.9
Hispanic	393	14.3
Other	10	0.3
Unknown	49	1.8
Total	2753	100.0

Source: From AIDS Activity Center for Infectious Diseases [13].

TABLE VI. *Acquired immune deficiency syndrome (AIDS): Weekly surveillance report of U.S. cases reported to CDC (November 15, 1983)*

Patient characteristics	Males		Females		Total	
	Cases	Percent	Cases	Percent	Cases	Percent
Homosexual or bisexual	1964	76.5	0	0.0	1964	71.3
Intravenous (IV) drug users	374	14.6	99	53.5	473	17.2
Haitian	113	4.4	18	9.7	131	4.8
Hemophiliac	18	0.7	0	0.0	18	0.6
None apparent/unknown	99	3.8	68	36.8	167	6.1
Total	2568	100.0	185	100.0	2753	100.0

Source: From AIDS Activity Center for Infectious Diseases [13].

TABLE VII. *No risk factors—130 cases (June 1981 through September 1983)*

	No. of cases (%)
Transfusion in previous 5 years	22 (17%)
Sexual partners of cases	20 (15%)
Background opportunistic infections	15 (12%)
Background Kaposi's sarcoma	13 (10%)
Typical AIDS with no known risk	60 (46%)

Source: From H Jaffee, personal communication.

TABLE VIII. *Acquired immune deficiency syndrome (AIDS): Weekly surveillance report of U.S. cases reported to CDC (November 15, 1983)*

Residence	No. of cases	Percent of total
New York State	1251	45.4
New York City	1060	38.5
Other, New York	191	6.9
California	599	21.8
San Francisco	333	12.1
Los Angeles	203	7.4
Other, California	63	2.3
Florida	204	7.4
Miami	124	4.5
Other, Florida	80	2.9
New Jersey	170	6.2
Newark	77	2.8
Other, New Jersey	93	3.4
Texas	87	3.1
Illinois	50	1.8
Pennsylvania	49	1.8
Massachusetts	38	1.4
Georgia	33	1.2
Connecticut	26	0.9
Colorado	25	0.9
Maryland	25	0.9
Virginia	24	0.9
Washington, D.C.	22	0.8
Ohio	15	0.5
Puerto Rico	13	0.5
Louisiana	12	0.4
Arizona	10	0.4
South Carolina	10	0.4
Other states (26)	90	3.3
Total—United States	2753	100.0

Source: From AIDS Activity Center for Infectious Diseases [13].

of society. Jaffee has analyzed the first 130 cases with no apparent risk factors from 1981 through September of 1983. As can be seen in Table VII, about 30% of the cases were exposed to either blood or blood products or were the sexual partners of individuals with AIDS. Twenty percent of the cases appeared to represent background infections or background cases of Kaposi's sarcoma. About 50% had typical AIDS with no known risk factors. It should be noted, however, that many of these cases were dead when this study was done and, consequently, detailed sexual and social histories were impossible to obtain.

Table VIII shows the number of cases in the United States by state. Half the cases have been reported from New York and New Jersey, with 20% from California and 7% from Florida.

An increasing number of foreign countries have begun to report cases of AIDS. As of November 15, 1983, 50 cases had been reported from Canada, with an epidemic pattern almost identical to that seen in the United States. Table IX shows the European cases reported as of October 20, 1983. Twenty-two percent of the 268 European cases were individuals born in Africa. Of the African cases, 37% were women. This is particularly significant. In the United States and Canada and among Europeans with AIDS, only about 5% of the cases have occurred in women. Reports from Haiti and Zaire and the African cases reported from Europe indicate a much higher incidence of the disease in women from these areas.

The excellent and illustrative data compiled by Professor Koch and his colleagues of the Robert Koch Institute in Berlin (Fig 1) clearly show that the epidemic of AIDS in San Francisco and in West Germany parallels the epidemic in New York, with an identical incidence rate separated only by time.

The situation in Haiti and Zaire is less clear. The epidemic was noted in Haiti in 1979, and as of November 1983, 202 cases have been reported. Most of the patients are in their midthirties, with 85% men and 15% women [15]. It is not yet clear if the mode of transmission is the same in Haiti as that noted in

TABLE IX. *Cases of AIDS reported to the European regional office of the World Health Organization (October 20, 1983)*

Country	79	1979	1980	1981	1982	1983	Total
Austria						7	7
Belgium			2	4	8	24	38
Czechoslovakia					1	1	2
Finland						2	2
France	6	1	5	5	30	47	94
West Germany	1	1			7	33	42
Ireland						2	2
Italy	1				2		3
Netherlands					3	9	12
Norway						2	2
Spain				1	1	4	6
Sweden					1	3	4
Switzerland			2	3	5	7	17
United Kingdom				2	5	17	24
Total	8	2	10	17	67	164	268[a]

[a] East Germany, Greece, Hungary, Luxembourg, Poland, USSR, and Yugoslavia reported no cases. No information was received from other countries.

Source: From European Regional Office of World Health Organization [14].

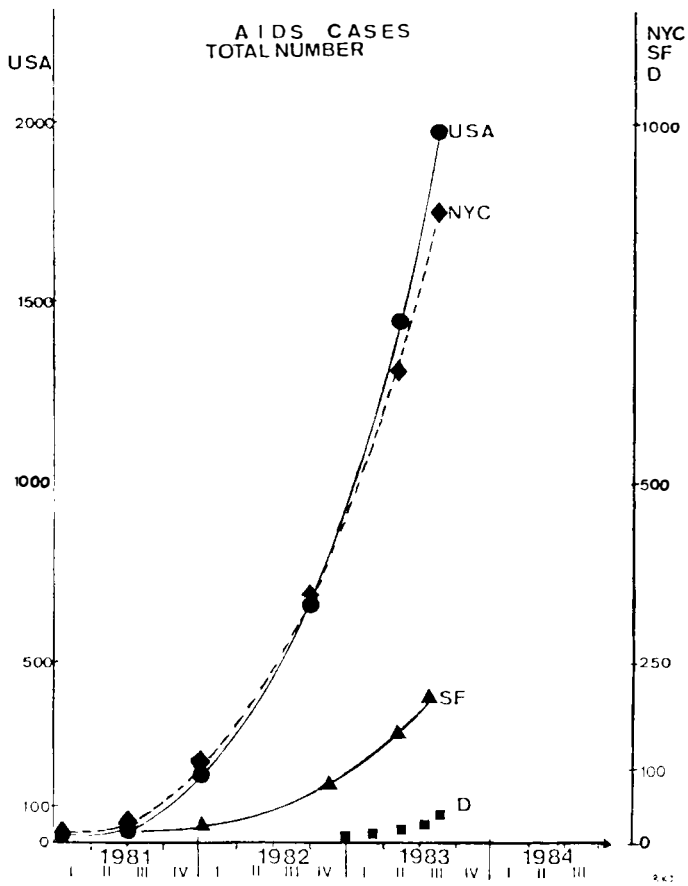

FIG 1. Travel histories to the United States, Haiti, and Africa (last 5 years, written reports).

the United States and Canada. Forty-nine cases were described in Kinshasa, Zaire, in the fall of 1983. Forty-one percent of these cases were women. Comparisons between American and European cases and Haitian and African cases must be made with great caution. The two areas are not comparable because of different standards of living, different cultural mores, and different availabilities of trained health care professionals. In Haiti and Zaire, intractable diarrhea and progressive tuberculosis appear to be the two most common manifestations of AIDS, followed by esophygeal candidiasis and toxoplasmosis. *Pneumocystis* pneumonia is seen less frequently and Kaposi's sarcoma is rare. This is clearly a different pattern of disease than that reported in the United States and Europe, but it may represent the same syndrome in a developing nation.

WHAT IS THE CAUSE OF AIDS?

Early attempts to explain this new epidemic centered on investigations of the lifestyles of patients with reported cases in the hope of finding some environmental factor (such as the recreational drug amyl nitrate), or repeated exposure to sexually transmitted diseases, or treatment of one of these sexually transmitted diseases that might suppress the immune system of individuals and allow the opportunistic infection or the opportunistic malignancy to appear. Unfortunately, no environmental factor was easily demonstrable. Indeed, as the epidemic grew, it became more and more apparent that the epidemiologic pattern was similar to the groups at risk for acquiring hepatitis B. The groups at risk for hepatitis B are male homosexuals, prostitutes, intravenous drug abusers, prisoners, family members of individuals with hepatitis B infection, infants of mothers with hepatitis B infection, residents and staff of institutions for the mentally retarded, patients and staff of hemodialysis units, hemophiliacs, nurses, physicians, medical students, and oral surgeons. AIDS has been diagnosed in most of these groups. In the fall of 1983, 76% of all of the AIDS patients gave a history of homosexual or bisexual behvior, 15% of the patients were intravenous drug users, 1% of the patients were hemophiliacs, and 3–5% of the patients did not fall into any known risk group [16]. The disease had been seen in homosexual prisoners [17], and one case of an infant who received an exchange transfusion of blood that was donated by a healthy homosexual man who later developed AIDS has been reported. Dr. Arthur Ammann has reported four infants born of an intravenous drug abusing mother who show evidence of AIDS [18–20], and an increasing number of cases are being described in women whose only risk factors appear to be that their sexual partners are either intravenous drug abusers or bisexual men [21]. AIDS has occurred in health care providers, but all these individuals appear to be homosexual men. No case of AIDS in a health care provider has yet been directly linked to exposure to a patient suffering from the disease [19]. Unfortunately, if the mode of transmission is by exposure to blood or blood products, we can expect to eventually see a case of AIDS in a health care worker who accidentally inoculates himself or herself by an inadvertent needle stick.

The parallels between the individuals who develop the acquired immune deficiency syndrome and those at risk for developing hepatitis B are so strong that most investigators currently favor the hypothesis that AIDS is caused by a bloodborne sexually transmitted agent that has newly been introduced into extremely high risk populations—namely, sexually promiscuous homosexual men and intravenous drug abusers.

WHAT IS THE AIDS AGENT?

Everything that we know about the AIDS epidemic is based on epidemiologic information. To date, no one has isolated the AIDS agent, and no laboratory test has been developed that clearly delineates those individuals who have been infected from those who have not. The most likely candidate is a yet unidentified retrovirus not previously introduced into the at risk population, where it is currently spreading at an exponential rate. This agent may have existed in some animal other than humans for centuries, but previous inoculation of humans was unrecognized and did not lead to the introduction of the agent into a high-risk group. If this is true, then adaptation of the virus to its new host may still be occurring. The agent may become more or less virulent as adaptation progresses, but reports from physicians caring for patients with AIDS would suggest that changes have not yet been noted. The appearance of the opportunistic infections and opportunistic malignancies remains the same, and the complications and death rate from the disease appear the same today as when the epidemic was first noted in 1980.

The mode of spread of the agent also remains unchanged. An analysis of the first 500 cases of AIDS that occurred in the 4 years between 1978 and 1982 and the last 500 cases that occurred in the 4 weeks of September 1983 shows that the same percentage of cases are homosexual men, intravenous drug users, hemophiliacs, and Haitians in the first 500 cases and in the last 500 cases. This strongly suggests that the epidemic is not spreading to other groups in the population.

A popular hypothesis has held that the AIDS agent is the one responsible for the endemic focus of Kaposi's sarcoma that has been known in Africa for years. A variety of arguments can be mounted against this theory. First, as seen in Table X, the clinical presentation and course of Kaposi's sarcoma in Africa have many features quite different from those seen in endemic Kaposi's sarcoma. Second, while case histories in certain rural parts of Africa are extremely difficult to obtain, the number of deaths from *Pneumocystis* pneumonia and other opportunistic infections seen in the AIDS epidemic are not occurring with the same frequency in Africa. Finally, had the disease been present in Africa for many years, earlier exposure to the homosexual community or to an intravenous drug abuser should have occurred.

Human T-cell leukemia virus (HTLV) has recently been linked to AIDS by investigators from Harvard, the National Cancer Institute, and the Institute Pasteur. Feline leukemia virus is known to be associated with prolongation of allograft rejection, thymic atrophy, depletion of paracortical lymphoid tissue, decreased response to T-cell mitogens, and depressed peripheral blood lymphocyte counts [22]. Indeed, cats infected with feline leukemia virus die more frequently from opportunistic infections than from leukemia. Essex and McLane, at Harvard, have shown antibodies against membrane-associated antigens of HTLV in 30% of 75 patients with AIDS [23]. Gelmann and Popovic were able to demonstrate viral DNA in the cells of 2 of 33 AIDS patients [24].

Finally, Luc Montagnier, of the Institute Pasteur, has isolated a new strain of HTLV from a homosexual male who appears to suffer from the gay lymph node syndrome, which is considered by many to represent an individual who has been infected with the AIDS agent but the only manifestation of the disease is mild leukopenia, marked helper T-cell depression (0.8:1), and reactive hyperplasia of posterior cervical and axillary lymph nodes. Human T-cell leukemia virus, which was initially described in 1981, was first isolated from an American patient with mycosis fungoides. Subsequently, the same virus was found in individuals with lymphoid malignancies in the United States, the Caribbean, and southern Japan. Another malignancy known to be caused by human T-cell leukemia

TABLE X.

	Classical	African	AIDS
Cutaneous location	Lower legs	Extremities	Generalized
Mucosal involvement	Rare	Rare	Common
Node involvement	Rare	Uncommon	Frequent
Indolent course	Common	Common	Unusual
Response to treatment	Excellent	Excellent	Poor

virus is hairy cell leukemia. This malignancy however, is caused by a second strain of HTLV. The agent isolated at the Institute Pasteur in the man with the gay lymph node syndrome would appear to be a third strain of HTLV virus [25].

A DNA arbovirus transmitted by ticks to wild swine in Africa was recently suggested as a possible etiologic agent for AIDS by Dr. Jame Teas [26]. Dr. Teas points out that the epidemic of African swine fever virus appeared in Haiti at about the same time that the AIDS epidemic occurred. She postulates that this highly variable agent infected individuals who consumed uncooked pork. Early studies looking for antibodies to African swine fever virus have failed to demonstrate antibodies in AIDS patients.

Dr. Larry Drew and coworkers [27] demonstrated that 94% of homosexual males and only 54% of heterosexual males showed past infection with cytomegalovirus. For this reason, an early theory was that the immunosuppression of AIDS was caused by a new and virulent mutant of cytomegalovirus. It is known that cytomegaloviral infection can cause cervical lymphadenopathy similar to that seen in patients with the gay lymph node syndrome and that marked helper T-cell depression can occur for up to 8 months following cytomegaloviral mononucleosis. While most patients with AIDS show active cytomegaloviral infection, endonuclease restriction enzyme analysis shows a variable pattern of cytomegalovirus (CMV) infection in gay men and does not support the hypothesis that there is a single new mutant responsible for the current epidemic. Drew's original work on the prevalence of cytomegalovirus infection in homosexual men was done before the AIDS epidemic was seen in San Francisco, and it is known that cytomegalovirus infections are common in homosexual men in numerous cities where cases of AIDS have not yet been seen. For these reasons, CMV is not considered a likely candidate as the AIDS agent.

Epstein-Barr virus (EBV) antibodies are elevated in most AIDS patients, and the virus has been recovered in some cases. The antibody patterns, however, suggest reactivation of a latent infection and not a newly acquired immunosuppressive disease.

Dr. Pieter J. de Jong and his colleagues, at the Albert Einstein College of Medicine and the Montefiore Medical Center, have recovered 13 adenovirus isolates from 10 patients with AIDS. Endonuclease restriction enzyme analyses of these isolates show 12 to be adenovirus-35 and 1 to be adenovirus-34. Adenovirus is known to remain in tonsillar tissue for long periods after infection. However, reactivation in an immunosuppressed individual should show a variety of the 39 known serotypes of adenovirus and not be limited to just serotype 35. Our group in San Francisco is recovering adenovirus in the semen of about 12% of all immunosuppressed homosexual men seen in our clinics. These isolates are currently being serotyped.

Parvovirus is an attractive agent as the cause of AIDS. This small DNA virus is known to cause Aleutian mink disease, which is characterized by clinical features suggestive of AIDS, including generalized lymphadenopathy, progressive immune complex disease, the production of autoantibodies, and progressive polyclonal hypergammaglobulinemia. Genetic predisposition is critical to Aleutian mink disease. This disease is universally fatal to Aleutian mink, but other species of mink are not susceptible. Parvovirus appeared de novo in the canine population of this country in 1972 and has caused widespread mortality and morbidity among household pets. The sudden appearance of this agent in dogs underscores the fact that a new viral agent can suddenly appear and spread in a susceptible population, much as we have seen in the AIDS epidemic.

No single agent has yet been incriminated as the cause of acquired immune deficiency syndrome. Individuals suffering from AIDS are at risk of acquiring a variety of opportunistic infections, including viral infections. Further, because of the profound immunosuppression, reactivation of a previous viral infection is possible. Confirmation that some virus is the cause of this new disease will require demonstration of antibodies to the virus in a large percentage of patients with AIDS and the gay lymph node syndrome and a demonstration of the same viral agent in AIDS patients from different geographic locations.

DOES CYTOMEGALOVIRUS CAUSE KAPOSI'S SARCOMA?

While it does not appear that cytomegalovirus is the agent responsible for the severe immunosuppression characteristic of AIDS, it may well be that this virus in a severely immunocompromised individual may be the etiologic factor responsible for the appearance of the opportunistic malignancy Kaposi's sarcoma. In the 1970s, Giraldo was able to demonstrate cytomegalovirus from some African cases of Kaposi's sarcoma [28]. However, the African Kaposi's sarcoma patients failed to demonstrate a serologic association between Kaposi's sarcoma and cytomegalovirus. A subsequent study by Giraldo showed serologic association between cytomegalovirus antibodies and the presence of Kaposi's sarcoma in American patients [29]. In this study there was an association between CMV antibodies and Kaposi's sarcoma as opposed to the presence of CMV antibodies in melanoma patients. The study was not statistically significant, however, because of the high background incidence of cytomegalovirus infection in the control population.

In 1972, Giraldo demonstrated typical herpes-like virus particles in 5 of 8 tissue culture lines derived from cases of Kaposi's sarcoma [28]. In work that we have done at the University of California, San Francisco, we have not been able to demonstrate cytomegalovirus or any other virus in material taken from cutaneous lesions of epidemic Kaposi's sarcoma or from 4 cases of traditional Kaposi's sarcoma [30]. Ewing and associates [31] have shown vesicular rosette structures in the lymph nodes of 17 of 18 patients with gay lymph node syndrome and 3 of 6 patients who died of AIDS. Whether these unusual structures represent some infectious agent or will prove to be some type of artefact is still controversial.

Drew [32] showed CMV IgG in 9 of 9 homosexual men with epidemic Kaposi's sarcoma and CMV IgM in 7 of 9 of the same patients. Cytomegalovirus was recovered from the semen or blood of 7 of 10 of these patients. Kaposi's sarcoma tumor tissue was cultured for cytomegalovirus. Eight of 8 cultures were negative; however, 6 of 9 tumors showed CMV DNA antigens, and 2 of 3 tumors showed CMV RNA by in situ hybridization. These findings suggest that not only is CMV DNA present in the tumor of Kaposi's sarcoma, but it is also demonstrating activity by encoding for CMV messenger RNA. As with the association that has been demonstrated between herpes type II and cervical cancer, these findings do not prove that CMV is the cause of Kaposi's sarcoma, but they clearly show a strong relationship between this virus and the malignancy.

The AIDS epidemic is just beginning and has already caused extreme suffering and the needless deaths of large numbers of young adults. The cost to society has been great and may be staggering before this disease can be contained. Hopefully, out of this calamity we will gain greater insights into how viral agents suppress normal immune function and clarify the role of cytomegalovirus in the etiology of Kaposi's sarcoma.

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